J. Clin. Chem. Clin. Biochem.
Vol. 15, 1977, pp. 549–551

Influence of Drugs on Clinical Chemical Data for Serum Glucose, Investigated with the Automated Glucose Oxidase-Perid Method

By *Mira Keler-Bačoka* and *Andrina Stojanovski-Bubanj*

Institute of Medical Biochemistry, Clinic for Internal Diseases, Medical Faculty, University of Zagreb, Zagreb, Rebro, Yugoslavia

(Received December 13, 1976/April 7, 1977)

Summary: Fifty drugs, applied in the therapy of internal diseases, were investigated for their effect on the clinical chemical determination of serum glucose by the automated GOD-Perid method. The results showed a statistically significant depression of the reported glucose value, by 7 drugs containing the pyrazolone group and its derivates (Baralgin, Butazolidine, Analgin, Novalgetol, Analgocain, Irgapyrin, Aminopyrin) $P < 0.001$; $P < 0.01$. The influence depends on the quantity of drug and on the time interval between loading and glucose analysis.

Einfluß von Arzneimitteln auf klinisch-chemische Serumglucose-Ergebnisse, untersucht mit der automatisierten GOD-Perid Methode

Zusammenfassung: Es wurde der Einfluß von 50 Arzneimitteln, welche in der Therapie innerer Krankheiten Anwendung finden, auf klinisch-chemische Ergebnisse für Serumglucose, erhalten mit der automatisierten GOD-Perid Methode, geprüft. Die Ergebnisse zeigen einen statistisch signifikanten ($P < 0{,}001$; $P < 0{,}01$) erniedrigenden Einfluß von 7 Arzneimitteln, welche die Pyrazolongruppe und deren Derivate enthalten (Baralgin, Butazolidin, Analgin, Novalgetol, Analgocain, Irgapyrin, Aminopyrin) auf die Glucosewerte. Der Einfluß ist von der Arzneimittelmenge sowie vom Zeitintervall zwischen Applikation und Glucoseanalyse abhängig.

Introduction

Clinical chemical data for blood glucose, determined with specific glucose-oxidase reactions, are influenced by ascorbic acid (1, 2), hydrogen-peroxide and hypochlorite (3), diuretics and some other drugs (4). The interference of the sulphonylurea drugs, Tolazamide and Tolbutamide, in the determination of glucose by the GOD-Perid method has been described (5, 6), and it is a consequence of the lack of specificity of the final chromogen color reaction of this analytical procedure. Reducing substances either compete with the chromogen for H_2O_2 or keep it in reduced state leading to low glucose values (6). With regard to published data (1–6) and to our observation on the serum glucose depressing effect of Baralgin, the aim of this work was to investigate drugs, applied in the therapy of internal diseases, for their possible influence on serum glucose data, estimated with the GOD-Perid method. Simultaneously the influence of drugs on serum urea data was investigated.

Material and Methods

The analyses were performed in clear, nonhemolyzed, fasting sera and in glucose water solutions before and after in vitro loading with each of the 50 drugs listed in table 1.

Most of the investigated drugs were in solution for intravenous application, except the oral tablet drugs Tolbusal, Meldian, Buformin, Daonil and Thyralette. The loading of sera and glucose solution 5.55 mmol/l (100 mg/dl) was performed by dilution of the ampule contents with serum in the proportions found in 3000 ml plasma 3 min after intravenous application, or by suspending 1 pulverized tablet in 3000 ml serum.

Parallel analyses of glucose in unloaded and drug-loaded material were performed on the Autoanalyzer I Technicon with the GOD-Perid ABTS test[1]), where in the final colorimetric reaction the redox chromogen indicator ABTS (2,2'-Azino-di-(3-ethyl-benzthiazoline-6-sulphonic acid)) (7) is used. To investigate the eventual interference of 50 drugs (table 1) on urea results, analogous experiments in sera and urea solution (0.83 mmol/l; 50 mg/dl) were performed. Urea was analyzed by the urease-hypochlorite procedure[2]).

[1]) Blood-Sugar GOD-Perid ABTS Biochemica Test Combination, Boehringer, Mannheim, Germany.

[2]) Urea Biochemica Test Combination, Boehringer, Mannheim, Germany.

Tab. 1. List of investigated drugs.

Therapeutic	Proprietary Name (International Nonproprietary Name, INN)
1. Cardiotonics:	Ceditanid, Lekozid, Lanicor (INN* Lanatozid C, Lanatozid C, Digoxin)
2. Antiarrhythmics:	Gilurytmal (INN Ajmaline)
3. Vasoconstrictors:	Adrenalin, Dihydroergotamin (INN Epinephrine, Dihydroergotamine mesilate)
4. Antihypertonics:	Serpasil (INN Reserpine)
5. Anticoagulants:	Heparin (INN Heparin)
6. Diuretics:	Lasix (INN Furosemide)
7. Antidiabetics:	Insulin, Tolbusal, Meldian, Buformin, Daonil (INN Insulin, Tolbutamide, Chloropropamide, Buformin hydrochloride, Glibenclamide)
8. Antineoplastics:	Antimit, Endoxan, Oncovin, Vinblastin, Daunoblastina (INN Chlormethine hydrochloride, Cyclophosphamide, Vincristine sulfate, Daunorubicin hydrochloride)
9. Sulfonamides:	Sulfazol (INN Sulfafurazol)
10. Antiemetics:	Reglan (INN Metoclopramide)
11. Antihistaminics:	Phenergan (INN Promethazine hydrochloride)
12. Vitamins:	Plivit C, Plivit B1, Plivit B6, Plivit B12, Vitamin K1 (INN Ascorbic. acid., Thiamine hydrochloride, Pyridoxine hydrochloride, Cyancobalamin, Phytometadion)
13. Hormones:	Progesterone, Testosterone, Femandren M, Ultracorten, Thyralette (INN Progesterone, Testosterone, Estradiol benzoate – Testosterone isobutyrate, Prednisone, Levothyroxine sodium)
14. Antibiotics:	Ceporin, Penbritin, Streptomycin, Geomycin, Eritromicin, Garamycin, Kanamicin, Kemicetin, Vibramycin (INN Cefaloridine, Ampicillin, Streptomycin, Oxytetracycline, Erythromycin, Gentamycin sulfate, Kanamycin, Chloramphenicol, Doxycycline hyclate)
15. Sedatives:	Apaurin (INN Diazepam)
16. Anesthetics:	Lidocain (INN Lidocaine)
17. Hypnotics:	Phenobarbitone (INN Phenobarbital)
18. Spasmolytics:	Baralgin (INN Fenpiverinium bromide-Noramidopyrinium methanesulfonate sodium-Pitofenone)
19. Analgetics:	Butazolidin, Irgapyrin, Aminopyrin, Analgin, Novalgetol, Analgocain (INN Phenylbutazone, Aminophenazone – Phenylbutazone, Aminophenazone, Noramidopyrinium methanesulfonate sodium, Noramidopyrinium methanesulfonate sodium, Noramidopyrinium methanesulfonate sodium – Lidocaine)

*) World Health Organization
International monitoring of adverse reactions to drugs
Drug Reference List No 13, 1975.
Suppl. No 1, 2, 3 Ref. No 271, 279, 287, 1976.

Experiments and Results

50 drugs were investigated. 7 drugs containing pyrazolone, pyrazolidine, phenazone or butazone and 2 drugs incorporating ascorbic acid (fig. 1, tab. 2) caused a de-

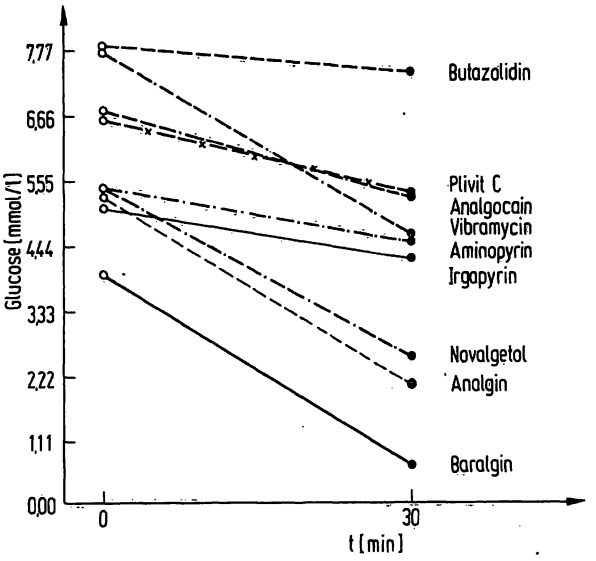

Fig. 1. Influence of 9 investigated drugs interfering with serum glucose data. ○ Sera, ● Loaded sera.
For INN see tables 1, 2.

Tab. 2. Drugs interfering with serum glucose values.

Drug	Formula	Interference
1. Plivit C amp. "Pliva"	500 mg sodium ascorbate	+
2. Vibramycin amp. "Pfizer"	100 mg doxicyclin, 480 mg ascorbic acid	+
3. Baralgin amp. "Jugoremedija"	2500 mg sodium-phenyl-dimethyl-pyrazolon-methyl-aminomethan-sulphonate + 10 mg *p*-piperidinoethoxy-*o*-carbmethoxy-benzophenon-hydrochloride + 0.10 mg diphenylpiperidinoethyl-acetamid-brom-methylatum	+
4. Butazolidin amp. (Phenylbutazon) "Geigy"	600 mg 1,2 diphenyl-3,5-dioxo-4-N butyl pyrazolidin sodium (phenylbutazon sodium) + 30 mg diethyl-aminoacet-2,6-*o*-xylidid	+
5. Analgin amp. "Pliva"	2500 mg nor-amino-phenazonemesilas sodium	+
6. Novalgetol amp. "Galenika"	2500 mg sodium-1 phenyl-2,3-dimethyl-3-pyrazolin-5 on-4-methyl-aminomethansul-phonate	+
7. Analgocain amp. "Galenika"	2500 mg nor-aminophenazone mesilas sodium + 25 mg lidocain hydrochloride	+
8. Irgapyrin amp.	450 mg 1–2 diphenyl-3,5 dioxo-4-N buthyl pyrazolidin sodium + 450 mg l-phenyl-2,3-dimethyl-4-dimethylamino-pyrazolon + 30 mg diethyl-aminoacet-2-*o*-xylidid	+
9. Aminopyrin tbl. "Krka"	300 mg aminophenazone	+

crease in the measured value for serum glucose. Since Baralgin showed the greatest effect (fig. 1), further experiments were performed with 85 mg Baralgin per 100 ml of serum or glucose solution. Statistical evaluation of 32 serum glucose data before ($\bar{x} \pm s = 4.94 \pm 1.17$ mmol/l) and 30 min after loading ($\bar{x} \pm s = 0.79 \pm 0.62$ mmol/l) demonstrated a statistically significant glucose depressing effect of Baralgin of ($P < 0.001$). The difference between mean glucose values in unloaded and Baralgin-loaded sera was 4.15 mmol/l glucose.

The difference between mean glucose data for glucose solutions of 5.55, 11.11, 16.65, and 22.22 mmol/l before and after Baralgin-loading was found to be 2.89 mmol/l.

The addition of 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100 mg of Baralgin to 100 ml serum or glucose solution (5.55 mmol/l) showed a direct relationship between the Baralgin concentration and its depressing influence on the glucose data. Glucose values were determined in 10 different sera ($\bar{x} = 4.03$ mmol/l) immediately, and 30, 60, and 120 min after loading with Baralgin. The glucose data were most depressed immediately after drug addition ($\bar{x} = 1.58$ mmol/l); after 30, 60, and 120 min the decrease was 0.58, 0.33 and 0.27 mmol/l glucose, respectively. None of the 50 investigated drugs affected the urea values in serum or urea solution.

Discussion

In this work it was showed that 7 drugs, containing pyrazolone or derivates lead to a decrease in the reported value for serum glucose, investigated with the GOD-Perid ABTS method. These drugs contain the hydrazine-N-N-group, which might have an acceptor function for the oxygen (5) derived from H_2O_2 in the GOD-Perid ABTS analytic procedure, and possibly inhibit the chromogen ABTS reaction. The effect depends upon the drug concentration in the serum, the time interval between drug-loading and glucose analysis, and probably on the type of substituent in the pyrazolone. These findings are in accordance with published data on the glucose depressing effect of drugs with a hydrazine group in close proximity to benzene nucleus (5). Some drugs might compete with the chromogen for H_2O_2 or keep it in reduced state, leading to GOD-POD reactions that are not specific for the glucose determination (6).

Our findings show that some unpublished pyrazolone drugs, depress GOD-Perid serum glucose values, and complete the list of other drugs with a similar effect described earlier (1–6). The interaction of ascorbic acid, in amounts greater than 16.6 mg in 100 ml serum, with glucose data is confirmed in this work, although no interference by amounts less than 5.0 mg ascorbic acid in 100 ml sera was observed earlier (9).

References

1. Caraway, W. T. (1965), Am. J. Clin. Pathol. *37*, 445–464.
2. Sharp, P. (1972), Clin. Chim. Acta *40*, 115–120.
3. Wirth, W. A. & Thompson, R. L. (1965), Am. J. Clin. Pathol. *43*, 579–590.
4. Elking, M. P. & Kabat, H. F. (1968), Am. J. Hosp. Pharm. *25*, 485–519.
5. Sharp, P., Reley, C., Cook, J. G. H. & Pink, P. J. F. (1972), Clin. Chim. Acta *36*, 93–98.
6. Caraway, W. T. & Kammeyer, C. W. (1972), Clin. Chim. Acta *41*, 395–434.
7. Werner, W., Rey, H. G. & Wiehlinger, H. (1970), Z. Anal. Chem. *252*, 224–228.
8. Fawcett, J. K. & Scott, J. E. (1960), J. Clin. Pathol. *13*, 156–159.
9. Keler-Bačoka, M., Stojanovski-Bubanj, A. & Blažević, K. (1971), Farm. glas. *27*, 367–370.

Prof. Dr. Mira Keler-Bačoka,
Institute of Medical Biochemistry,
Clinic for Internal Diseases,
Medical Faculty,
University of Zagreb,
Zagreb, Rebro,
Yugoslavia